BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PATENT SPECIFICATION (11) 1 569 286

1 569 286

(21) Application No. 44625/76 (22) Filed 27 Oct. 1976 (19)

(31) Convention Application No. 2548413 (32) Filed 27 Oct. 1975 in

(33) Fed. Rep of Germany (DE)

(44) Complete Specification Published 11 Jun. 1980

(51) INT. CL.[3] A61K 31/56

(52) Index at Acceptance
A5B 823 835 L

(54) OILY DEPOT SOLUTIONS OF GESTAGENS FOR INTRAMUSCULAR INJECTION

(71) We, SCHERING AKTIENGESELLSCHAFT, a Body Corporate organised according to the laws of Germany, of Berlin and Bergkamen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

The present invention is concerned with oily unsaturated depot solutions of gestagens, as hereinafter defined, for intramuscular injection and with their manufacture and use.

Depot preparations capable of being used for injection have already been known. As compared with preparations capable of being used for oral administration, they have the advantage that a single injection is sufficient for one or more months, whereas, for example, tablets must be taken daily. A depot effect is often brought about by adding the active substance to a carrier substance that slowly releases the active substance. An additional depot effect can be achieved by using a derivative of the active substance that decomposes to the active substance only in the body.

Depot preparations of gestagenic substances are used, for example, as contraceptive agents. Thus, for example, an oily solution of 17α-ethynyl-19-nor-testosterone oenanthate (norethisterone oenanthate) has been a clinically approved depot contraceptive for some years. At a dosage of 200 mg in 1 ml of castor oil/benzyl benzoate (6:4) the action lasts for 12 weeks. However, it has been found that the number of pregnancies is somewhat greater than in the case of taking oral tablets daily, and that undesired pregnancies occur especially shortly before the end of the injection-period. Moreover, it has been desired to obtain an action lasting for 13 weeks (3 months) because then the application-period can be calculated more easily in relation to the menstrual cycle.

It has now been found that a lengthening of the depot effect occurs when the volume of the injection solution is increased, while retaining the quantity of gestagen to be administered.

Female beagle hounds weighing about 13 kg were each injected simultaneously in the right and left M. glutaeus with 200 mg of 14.15-^{3}H-marked norethisterone oenanthate and 4-^{14}C-marked norethisterone oenanthate, respectively, in 1.8 ml and in 0.6 ml of castor oil/benzyl benzoate (6:4). During 13 weeks the ^{14}C- and ^{3}H-activity in the blood, plasma, urine and faeces was measured. The separation of the marked substances in proportion to the release from the depot showed up to 7 weeks after application no systematic difference between the selected volumes of application. There was found only a very small percentage reduction in the release during the initially high rates of release from the larger volumes. From the 8th week onwards the quantities of the marking applied with the larger volumes predominated. In the 13th week after application the release from the injection-volumes was increased in favour of the 1.8 ml solution by three and a half times, that is to say, in the 13th week there was observed, as compared with the smaller volumes, a rate of release about 3.5 times higher.

The measured quantities for the 13th week are given in the accompanying drawing.

It could not have been foreseen that, by increasing the volume of the solution while using the same quantity of gestagen, after intramuscular injection a retarded release of gestagen and therewith a lengthening of the duration of action would occur.

Owing to the lengthening of the period of action by increasing the injection-volume, a quantity of 200 mg of norethisterone oenanthate is sufficient for a reliable protection against conception for 3 months in women of child-bearing age. For a shorter or longer

period than 3 months smaller or larger quantities, respectively, of the gestagen are required. Generally, 50 to 500 mg, and preferably 200 to 400 mg, of norethisterone oenanthate, or corresponding quantities of another appropriate depot gestagen, are used in 1 to 6 ml, and preferably 2 to 4 ml, of oily solution. Lengthening of the period of action occurs even with a small increase in the volume; however, an advantageous increase in the volume of solvent is one and a half to three times (that is the concentration of active substance is 1/3 to 2/3 of that normally employed). A greater increase in the volume of solvent is basically possible within the scope of the present invention, but it is not recommended because such large volumes applied intramuscularly lead to trouble.

The present invention accordingly provides an oily solution of a gestagen, as hereinafter defined, the solution being suitable for use as a depot preparation by intramuscular injection and containing the gestagen in a maximum concentration as hereinafer defined.

The gestagen is understood herein to exclude any one of the following compounds, namely progesterone, 17α-hydroxy-progesterone and esters of 17α-hydroxy-progesterone.

The maximum concentration of the gestagen in the oily solution is understood herein to be a concentration having a gestagenic activity, as measured by its effect on the cervical mucus of a human female, corresponding to the gestagenic activity of substantially 133.33 mg per ml of norethisterone oenanthate in the same solvent.

The gestagen is advantageously present in a concentration that is 1/3 to 2/3 of the concentration of the gestagen normally used in an oily solution suitable for use as a depot preparation by intramuscular injection. In other words, a "preferred range of concentration" for the gestagen in the oily solution is a concentration having a gestagenic activity, as measured by its gestagenic effect on the cervical mucus of a human female, corresponding to the gestagenic activity of substantially 66.67 to 133.33 mg per ml of norethisterone oenanthate in the same solvent.

There are a number of properties of the cervical mucus of a human female affected by the administration of a gestagen which are well known to the gynaecologist, so that one or more such parameters can be used to correlate the gestagenic effect.

Gestagens are also known as gestogens, progestins, progestogens and progestational substances.

The present invention also provides a process for the manufacture of an oily solution of the present invention, wherein the gestagen is dissolved in an amount of the solvent sufficient to form a substantially saturated solution of the gestagen, the resulting solution is diluted with a further amount of the solvent and the resulting diluted solution is filtered under sterile conditions, and, if desired, the resulting solution is introduced into at least one ampoule under aseptic conditions and sterilized. The ampoule may have a capacity of 1, 2, 3 or 4 ml.

As gestagens there come into consideration one or more of these compounds that themselves, owing to their chemical structure, already display a protracted action when injected intramuscularly and for which, owing to their spectrum of action, a long lasting treatment is indicated. Such compounds are, for example, lipophilic steroid hormones and in this case especially steroid alcohols in the form of their esters. Oily solutions of these steroids having a gestagenic activity may be used, for example, for the control of fertility in human beings and animals or the treatment of menopausal complaints in women.

As gestagenic steroid hormones (gestagens) there may be mentioned, for example, esters of 19-nor-17-hydroxy-progesterone, and also esters of 17-hydroxy-progesterone derivatives, for example 17-esters of 6α-methyl-17-hydroxy-progesterone, 6-methyl-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-16α-methyl-17-hydroxy-progesterone, 6,16α-dimethyl-6-dehydro-17-hydroxy-progesterone, 1α,2α-methylene-6-chloro- or -6-fluoro-6-dehydro-17-hydroxy-progesterone or also esters of 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-18-methyl-19-nor-testosterone, 17α-ethynyl-Δ^4-oestrene-3,17β-diol or 17α-ethynyl-Δ^4-oestren-17β-ol. The gestagenic steroid hormone is advantageously 17α-ethynyl-19-nor-testosterone oenanthate.

The esters are derived from acids, for example carboxylic acids, capable of forming physiologically tolerable esters. Preferred are the esters of organic carboxylic acids containing at least 4 carbon atoms. The acids may belong to the aliphatic, cycloaliphatic, aromatic, aromatic-aliphatic or heterocyclic series. These acids may also be unsaturated and/or di- or poly-basic and/or substituted in the usual manner. As examples of substituents there may be mentioned alkyl, hydroxyl, alkoxy, oxo or amino groups or halogen atoms. There may be mentioned, for example, the following esters: butyrates, valerates, caproates, oenanthates, pelargonates, undecanoates, benzoates, β-cyclopentylpropionates and phenylacetates.

A 3-keto group present in the steroid hormone may be functionally converted and present, for example, as an enol-ester or enol-ether group. In the case of an enol-ester

group there also come into consideration the ester groups already mentioned above, but also acetates and propionates. In the case of an enol-ether group, the ether residue may be, preferably, a lower alkyl group, for example a methyl or ethyl group. Also suitable are cycloalkyl groups, for example a cyclopentyl or cyclohexyl group.

The effective dose of the gestagen in the oily solutions of the present invention depends on the purpose of the treatment, on the nature of the active substance and the desired duration of the action. It is, for example, for 17α-ethynyl-19-nor-testosterone oenanthate in the control of fertility in women for 3 months 200 mg. Instead of 17α-ethynyl-19-nor-testosterone oenanthate, there may be used comparable depot gestagens. The quantity of comparable gestagens administered and the frequency of their administration may be such that their gestagenic activity, as measured, for example, by their effect on the cervical mucus of a human female, corresponds to that produced by the administration of 200 mg of 17α-ethynyl-19-nor-testosterone oenanthate every three months.

The volumes intramuscularly injected of the oily solutions of the present invention are normally 1 to 6 ml. The oily solutions are thus advantageously made up in unit dosage form, each dosage unit having a volume within the range of from 1 to 6 ml, for example a volume of 1, 2, 3 or 4 ml. Each dosage unit may be contained in an ampoule.

It is advantageous for every 1 to 6 ml of the oily solutions of the present invention to contain 50 to 500 mg of the gestagen, and more especially for every 2 to 4 ml of the solutions to contain 200 to 400 mg of the gestagen.

As oily solvents there are suitable those known to the expert for such purposes, for example sesame oil and castor oil. For increasing the solubility of the gestagen there may be added to the oily solvents solubilizers, for example benzyl benzoate or benzyl alcohol. In addition to those mentioned above other vegetable oils, for example linseed oil, cottonseed oil, sunflower oil, ground nut oil, olive oil and wheat oil, may be used. Also suitable are synthetic oils, for example polyethylene glycol, triglycerides of higher saturated fatty acids and monoesters of higher fatty acids. A mixture of castor oil/benzyl benzoate in the ratio by volume of 6:4 is preferred as solvent.

As indicated above, the oily solutions of the present invention can be used as contraceptives.

The present invention accordingly further provides a method of contraception, wherein there is administered by intramuscular injection in a contraceptive dose to a female mammal, advantageously a female of the human species, an oily solution of a gestagen, as hereinbefore defined, the solution being suitable for use as a depot preparation by intramuscular injection and containing the gestagen in a maximum concentration as hereinbefore defined.

The various details of the oily solutions of the present invention discussed above also, of course, apply to the oily solutions used in the method of contraception of the present invention. Thus, for example, an advantageous embodiment of the method of contraception of the present invention is the administration by intramuscular injection to a human female every 13 weeks of 1 to 6 ml of the oily solution, the 1 to 6 ml containing 50 to 500 mg of the gestagen, and preferably of 2 to 4 ml of the oily solution, the 2 to 4 ml containing 200 to 400 mg of the gestagen.

The present invention further provides a contraceptive pack which comprises an oily solution of a gestagen, as hereinbefore defined, together with instructions, the instructions requiring the administration by intramuscular injection of the solution in a contraceptive dose to a female mammal, advantageously a female of the human species, and the solution being suitable for use as a depot preparation by intramuscular injection and containing the gestagen in a maximum concentration as hereinbefore defined.

The various details of the oily solutions of the present invention discussed above further apply to the oily solutions contained in the contraceptive packs of the present invention. Thus, the instructions in the packs advantageously require that there is administered to a human female every 13 weeks 1 to 6 ml of the oily solution, the 1 to 6 ml containing 50 to 500 mg of the gestagen, and preferably 2 to 4 ml of the oily solution, the 2 to 4 ml containing 200 to 400 mg of the gestagen.

The following Examples illustrate the invention:-

Example 1

2000 mg of 17α-ethynyl-19-nor-testosterone oenanthate were dissolved in a mixture of castor oil/benzyl benzoate (6:4 by volume), and the solution was then made up with a further amount of the same solvent to 20 ml. The solution was filtered under sterile conditions, and was introduced in the usual manner into 2 ml-ampoules under aseptic conditions. The ampoules were finally sterilized for 2 hours at 120°C.

Example 2

2000 mg of 17α-ethynyl-19-nor-testosterone oenanthate were dissolved in a mixture of castor oil/benzyl benzoate (6:4 by volume), and the solution was then made up with a further amount of the same solvent to 30 ml. The solution was filtered under sterile conditions, and was introduced in the usual manner into 3 ml-ampoules under aseptic conditions. The ampoules were finally sterilized for 2 hours at 120°C.

WHAT WE CLAIM IS:-

1. An oily solution of gestagen, as hereinbefore defined, the solution being suitable for use as a depot preparation by intramuscular injection and containing the gestagen in a maximum concentration as hereinbefore defined.
2. A solution as claimed in claim 1, wherein the gestagen is present in a preferred range of concentration as hereinbefore defined.
3. A solution as claimed in claim 1 or 2, which contains as the solvent a mixture of castor oil and benzyl benzoate.
4. A solution as claimed in claim 3, wherein the castor oil and benzyl benzoate are present in the mixture in the ratio by volume of 6:4.
5. A solution as claimed in any one of claims 1 to 4, wherein the gestagen is at least one lipophilic steroid.
6. A solution as claimed in claim 5, wherein the lipophilic steroid is a physiologically tolerable carboxylic acid ester of a steroid alcohol.
7. A solution as claimed in claim 6, wherein the carboxylic acid contains at least 4 carbon atoms.
8. A solution as claimed in any one of claims 1 to 7, wherein the gestagen is an ester of 19-nor-17-hydroxy-progesterone, 6α-methyl-17-hydroxy-progesterone, 6-methyl-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-16α-methyl-17-hydroxy-progesterone, 6,16α-dimethyl-6-dehydro-17-hydroxy-progesterone, 1α,2α-methylene-6-chloro- or -6-fluoro-6-dehydro-17-hydroxy-progesterone, 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-18-methyl-19-nor-testosterone, 17α-ethynyl-Δ^4-oestrene-3,17β-diol or 17α-ethynyl-Δ^4-oestren-17β-ol.
9. A solution as claimed in claim 8, wherein the gestagen is 17α-ethynyl-19-nor-testosterone oenanthate.
10. A solution as claimed in any one of claims 1 to 9, wherein every 1 to 6 ml of the solution contains 50 to 500 mg of the gestagen.
11. A solution as claimed in claim 10, wherein every 2 to 4 ml of the solution contains 200 to 400 mg of the gestagen.
12. A solution as claimed in any one of claims 1 to 11, which is in unit dosage form.
13. A solution as claimed in claim 12, wherein each dosage unit has a volume within the range of from 1 to 6 ml.
14. A solution as claimed in claim 13, wherein each dosage unit has a volume of 1, 2, 3 or 4 ml.
15. A solution as claimed in any one of claims 12 to 14, wherein each dosage unit is contained in an ampoule.
16. A solution as claimed in claim 1 having a composition substantially as described in Example 1 or 2 herein.
17. A process for the manufacture of an oily solution as claimed in any one of claims 1 to 16, wherein the gestagen is dissolved in an amount of the solvent sufficient to form a substantially saturated solution of the gestagen, the resulting solution is diluted with a further amount of the solvent and the resulting diluted solution is filtered under sterile conditions, and, if desired, the resulting solution is introduced into at least one ampoule under aseptic conditions and sterilized.
18. A process as claimed in claim 17, conducted substantially as described in Example 1 or 2 herein.
19. A method of contraception, wherein there is administered by intramuscular injection in a contraceptive dose to a female mammal an oily solution of a gestagen, as hereinbefore defined, the solution being suitable for use as a depot preparation by

intramuscular injection and containing the gestagen in a maximum concentration as hereinbefore defined.

20. A method as claimed in claim 19, wherein the gestagen is present in the oily solution in a preferred range of concentration as hereinbefore defined.

21. A method as claimed in claim 19 or 20, wherein the oily solution contains as the solvent a mixture of castor oil and benzyl benzoate.

22. A method as claimed in claim 21, wherein the castor oil and benzyl benzoate are present in the mixture in the ratio by volume of 6:4.

23. A method as claimed in any one of claims 19 to 22, wherein the gestagen is a physiologically tolerable, lipophilic carboxylic acid ester of a steroid alcohol.

24. A method as claimed in claim 23, wherein the carboxylic acid contains at least 4 carbon atoms.

25. A method as claimed in any one of claims 19 to 24, wherein the gestagen is an ester of 19-nor-17-hydroxy-progesterone, 6α-methyl-17-hydroxy-progesterone, 6-methyl-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-16α-methyl-17-hydroxy-progesterone, 6,16α-dimethyl-6-dehydro-17-hydroxy-progesterone, 1α-2α-methylene-6-chloro- or -6-fluoro-6-dehydro-17-hydroxy-progesterone, 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-18-methyl-19-nor-testosterone, 17α-ethynyl-18-methyl-19-nor-testosterone, 17α-ethynyl-Δ^4-oestrene-3,17β-diol or 17α-ethynyl-Δ^4-oestren-17β-ol.

26. A method as claimed in claim 25, wherein the gestagen is 17α-ethynyl-19-nor-testosterone oenanthate.

27. A method as claimed in any one of claims 19 to 26, wherein the female mammal is a female of the human species.

28. A method as claimed in claim 27, wherein there is administered to the human female every 13 weeks 1 to 6 ml of the oily solution, the 1 to 6 ml containing 50 to 500 mg of the gestagen.

29. A method as claimed in claim 28, wherein there is administered to the human female every 13 weeks 2 to 4 ml of the oily solution, the 2 to 4 ml containing 200 to 400 mg of the gestagen.

30. A method as claimed in claim 29, wherein there is administered to the human female every 13 weeks the contents of an ampoule having a composition substantially as described in Example 1 or 2 herein.

31. A contraceptive pack which comprises an oily solution of a gestagen, as hereinbefore defined, together with instructions, the instructions requiring the administration of intramuscular injection of the solution in a contraceptive dose to a female mammal and the solution being suitable for use as a depot preparation by intramuscular injection and containing the gestagen in a maximum concentration as hereinbefore defined.

32. A pack as claimed in claim 31, wherein the gestagen is present in the oily solution in a preferred range of concentration as hereinbefore defined.

33. A pack as claimed in claim 31 or 32, wherein the oily solution contains as the solvent a mixture of castor oil and benzyl benzoate.

34. A pack as claimed in claim 33, wherein the castor oil and benzyl benzoate are present in the mixture in the ratio by volume of 6:4.

35. A pack as claimed in any one of claims 31 to 34, wherein the gestagen is a physiologically tolerable, lipophilic carboxylic acid ester of a steroid alcohol.

36. A pack as claimed in claim 35, wherein the carboxylic acid contains at least 4 carbon atoms.

37. A pack as claimed in any one of claims 31 to 36, wherein the gestagen is an ester of 19-nor-17-hydroxy-progesterone, 6α-methyl-17-hydroxy-progesterone, 6-methyl-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-17-hydroxy-progesterone, 6-chloro- or 6-fluoro-6-dehydro-16α-methyl-17-hydroxy-progesterone, 6,16α-dimethyl-6-dehydro-17-hydroxy-progesterone, 1α,2α-methylene-6-chloro- or -6-fluoro-6-dehydro-17-hydroxy-progesterone, 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-18-methyl-19-nor-testosterone, 17α-ethynyl-Δ^4-oestrene-3.17β-diol or 17α-ethynyl-Δ^4-oestren-17β-ol.

38. A pack as claimed in claim 37, wherein the gestagen is 17α-ethynyl-19-nor-testosterone oenanthate.

39. A pack as claimed in any one of claims 31 to 38, wherein the oily solution is in unit dosage form.

40. A pack as claimed in any one of claims 31 to 39, wherein the female mammal is a female of the human species.

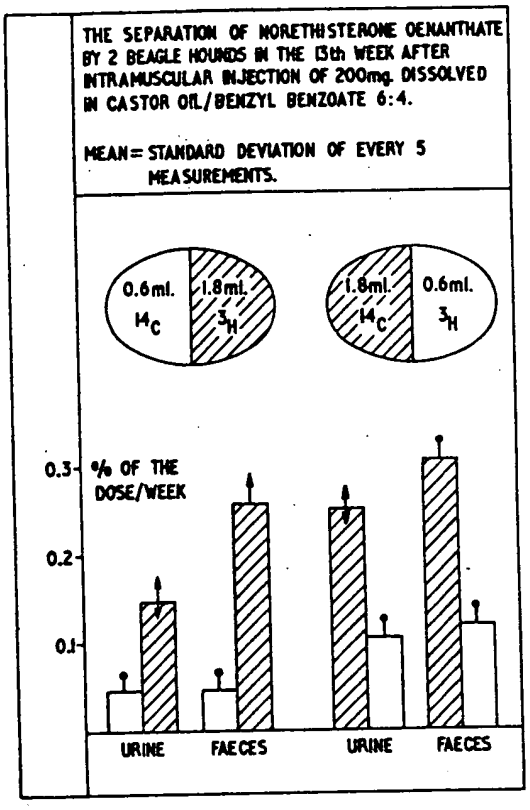
41. A pack as claimed in claim 40, wherein the instructions require that there is administered to the human female every 13 weeks 1 to 6 ml of the oily solution, the 1 to 6 ml containing 50 to 500 mg of the gestagen.

42. A pack as claimed in claim 41, wherein the instructions require that there is administered to the human female every 13 weeks 2 to 4 ml of the oily solution, the 2 to 4 ml containing 200 to 400 mg of the gestagen.

43. A pack as claimed in claim 31, wherein the oily solution is in unit dosage form, each dosage unit being contained in an ampoule and the ampoule having a composition substantially as described in Example 1 or 2 herein, and the instructions require that there is administered to a human female every 13 weeks one of the dosage units.

ABEL & IMRAY.
Chartered Patent Agents.
Northumberland House,
303-306 High Holborn,
London WC1V 7LH.

Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon, Surrey, 1980.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.


THE SEPARATION OF NORETHISTERONE OENANTHATE BY 2 BEAGLE HOUNDS IN THE 13th WEEK AFTER INTRAMUSCULAR INJECTION OF 200mg. DISSOLVED IN CASTOR OIL/BENZYL BENZOATE 6:4.
MEAN= STANDARD DEVIATION OF EVERY 5 MEASUREMENTS.
0.6ml. 14C
1.8ml. 3H
1.8ml. 14C
0.6ml. 3H
% OF THE DOSE/WEEK
0.3
0.2
0.1
URINE
FAECES
URINE
FAECES